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Dated: November 8, 2005

Signature:

Marian L. Christopher
(Marian L. Christopher)

Docket No.: 532512000500
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Patent Application of:

Gregory M. LANZA et al.

Application No.: 09/774,278

Filed: January 30, 2001

For: ENHANCED ULTRASOUND DETECTION
WITH TEMPERATURE-DEPENDENT
CONTRAST AGENTS

Confirmation No.: 2535

Art Unit: 1617

Examiner: S. Sharareh

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Brief is filed in reply to an Examiner's Answer mailed 9 September 2005; the reply is thus due 9 November 2005.

At the foundation of the disagreement between appellants and the Examiner in the present application is the issue of claim construction. Appellants believe that the claims as properly interpreted are clearly free of the sole prior art reference cited, Østenson, *et al.* (U.S. 6,375,931) and should appellants' position on claim interpretation be accepted, it appears clear from the record that the Examiner would agree to withdraw the outstanding rejections for anticipation and obviousness.

There appears to be agreement that the disclosure of Østenson, *et al.*, relates to enhancing ultrasonic images by expanding the size of microbubbles used as contrast agents. Østenson's invention resides in effecting this increase in size by supplying, in addition to the composition containing a dispersion of microbubbles, a composition which contains a "diffusible component" that is expected to mix with the gas in the microbubbles and expand their size. (See, for example, column 2, lines 56, *et seq.*) An increase in temperature could also be employed to increase the size of microbubbles as quoted by the Examiner's Answer on page 5, from a paragraph that appeared to be the basis for comparison between what one might expect when a gas is heated with the method of Østenson's disclosure as elaborated in the succeeding paragraph in column 35, beginning at line 19.

In any event, there appears to be no dispute that the Østenson disclosure requires the contrast agent to be a dispersion of microbubbles of gas (even in the "comparative" examples where no diffusible component is present such as Example 5). The claimed invention, on the other hand, does not include gaseous microbubbles, an absolute requirement of Østenson's disclosure. The claims require that the nanoparticles used as contrast agents be in liquid form in all steps of the process, including during imaging. It is not only a requirement of the present claims that the nanoparticles be liquid contained in the emulsions administered, the nanoparticles must be liquid in steps (a) through (d) of claim 1 and all the steps in claim 18.

It is difficult on its face to see how "liquid nanoparticles" could be interpreted as meaning "gas microbubbles." While during prosecution, claims may be given their broadest *reasonable* interpretation, the interpretation suggested by the Examiner, respectfully, is very far from reasonable. It violates the principles of claim interpretation which require that the teachings of the specification be taken into account in interpreting claim language. When "liquid" is specifically

defined in the specification as requiring <10% of the volume be occupied by gas, it is not reasonable to interpret the term “liquid nanoparticles” to read on gaseous microbubbles.

The Examiner is correct that the basis on which claim interpretation rests in prosecution is not identical to that with regard to issued patents, which enjoy the presumption of validity. This was acknowledged in *Phillips v. AWH Corp.*, 415 F3d 1303, 75 USPQ2d 1321 (Fed. Cir. *en banc* 2005). But, as stated by the Court, the PTO “determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction ‘in light of the specification as it would be interpreted by one of ordinary skill in the art’” citing *In re Am. Acad. Sci. Tec. Center*, 367 F3d 1359, 70 USPQ2d 1827 (Fed. Cir. 2004). The *Phillips* Court further points out that 37 C.F.R. § 1.75(d)(1) requires that the application claims must

conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.

The claim interpretation urged by appellants is clearly based on a specific definition set forth in the specification and the distinction drawn in the specification between the invention and the prior art which includes the behavior of microbubbles in ultrasound imaging.

The specification makes it completely clear that the invention lies in the unexpected finding that the ultrasound image of a targeted substance is enhanced when targeted *liquid* nanoparticles are bound to it in contrast to the expected behavior when microbubble contrast agents are used. As set forth, for example, on page 3, in contrasting the invention to be described with the prior art, the application, referring to various disclosures, states

In such approaches, temperature changes would serve to convert the gaseous precursor to gaseous microbubbles and none of these earlier studies disclose or suggested changing the temperature of an ultrasound contrast agent *which remains in the liquid state* or using

the change in temperature of a non-gaseous contrast agent as the basis for enhancing ultrasound detection.

The application goes on to state on page 3, at line 25,

the inventors herein have succeeded in discovering that changing the temperature of nanoparticles which contain a nongaseous fluorocarbon liquid and which are bound to a target, produces a detectable change in acoustic reflectivity of the target.”

The invention is further explained on page 4, at lines 12-24, in essentially the same terms as those set forth in the claims.

Further evidence that the term “liquid” in the claims does not include microbubbles is set forth on page 8, at lines 17-24, which limits the amount of gas that could even incidentally occur in the nanoparticles to <10%. Such small amounts of gas in a nanoparticle hardly meet the definition of a microbubble.

In addition, in *In re Morris*, 44 USPQ2d 1023 (Fed. Cir. 1997) the Court acknowledged that since the prosecution history could be taken into account when the claims were ultimately interpreted, it should be given some weight during prosecution. In support of affirming the Board’s interpretation of the claims at issue in *Morris*, the Court looked at the prosecution history and stated that in the prosecution

never do the appellants particularly distinguish their claimed invention (as compared with their inventive concept, whatever that means) from the prior art. We interpret this as a veiled attempt to avoid potential future effects of prosecution history estoppel. Such evasiveness we cannot condone, particularly when the public must rely on the written record to define the resulting property right.

No such evasion has been attempted here. Appellants have specifically defined “liquid nanoparticles” as being liquid at all times during imaging and have defined “liquid nanoparticles” as being <10% by volume of gas. Thus, by virtue of this specific definition and specific disclaimer,

there can be no reasonable future interpretation that the claims include microbubbles of Østenson at the time imaging occurs.

It is therefore unreasonable, in light of the definition of “liquid” in the specification and the inclusion of the same word in the claims applied to the particles at all steps of the process, to conclude that appellants do not claim what they clearly mean.

Since Østenson is solely concerned with the behavior of gas microbubbles and the present invention requires liquid nanoparticles, no possible anticipation can be found, no matter what steps are employed with each of these two very different types of compositions.

There is also no basis for rejecting the claims as obvious since enhancing ultrasound images by virtue of enlarging microbubbles makes no suggestion about the effect of temperature on the image obtained using targeted liquid nanoparticles.

In short, the rejections as they have been articulated rely on an interpretation of the claims that is neither intended by the applicants (as has been repeatedly stated during prosecution) nor can be justified as a reasonable interpretation of the claims in light of the specification.

Appellants believe the foregoing should be sufficient to distinguish Østenson, but in the interest of a complete reply, appellants wish to respond briefly to the Examiner’s own response to the prior arguments.

In the Examiner’s first argument that “Ostensen (sic) must not (sic) contain gas before administration; rather, it can solely contain perfluorocarbons that are liquid at the room temperature and turn into gas after they are administered in vivo,” appellants assume that the Examiner means “need not” rather than “must not.” In any event, this is irrelevant since the compositions of

Østenson must be gas microbubbles at the time they are imaged and the compositions used in the claimed methods must be liquid nanoparticles at that time.*

With regard to the second argument that “Østenson teach the rise of temperature subsequent to the administration of ultrasound frequencies,” appellants find no such teaching in Østenson. Østenson does teach, as the Examiner points out, that by raising the temperature the size of microbubbles can be increased, but it does not follow from the teachings of Østenson that the brief enhancement of contrast described in Example 5, in column 39, for example, is due to any increase in temperature effected by ultrasound. Østenson is simply silent on this topic. It will be noted that the claims require that the temperature of the liquid nanoparticles must be raised sufficiently to produce a measurable enhancement in acoustic reflectivity; thus, any trivial changes in temperature that might be caused by ultrasound are not included within the scope of the claims. Appellants believe they are correct that the examples set forth in Østenson make no mention of temperature change due to ultrasound imaging.

* There is apparently some confusion created by Østenson’s inclusion of perfluorooctylbromide (which would not be a gas under any circumstances consistent with mammalian physiology) in column 8, lines 59-60, where it is listed, albeit improbably, as a diffusion agent, not as the gas in the gas dispersion and the inclusion of perfluoroheptanes in column 3, line 42, where this compound is listed as being in admixture with gases in the gaseous dispersion, not as the precursor for the gases themselves. Applicants are uncertain why these particular compounds are included in the disclosure of Østenson and believe that their inclusion is in error. But whether in error or not, in neither case are these compounds listed as the components which generate gaseous microbubbles.

In summary, it is apparent that if the claims are interpreted correctly to require that the nanoparticles in appellants' compositions be liquid at all times during the imaging process and that the change in temperature effected enhances the image while the nanoparticles are in liquid form at both temperatures, Østenson is completely irrelevant to the invention as claimed. Although the Examiner has somehow interpreted the claims, despite their specification of "liquid nanoparticles" to include gaseous microbubbles at some stage in the imaging process, the Examiner has indicated agreement with Summary of the Invention in appellants' brief, which includes the statement that "the change of temperature of nanoparticles that contain essentially only nongaseous fluorocarbon liquid and bound to a target results in detectable changes in acoustic reflectivity of the target." If that statement is agreed with, the Examiner's interpretation of the claims appears inconsistent. Reversal of the rejection of claims 1, 3, 7-8, 13, 17-18, 21, 25-26, 31, 35 and 68-77 is thus respectfully requested.

An oral hearing is requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532512000500.

Dated: November 8, 2005

Respectfully submitted,

By 

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